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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,355	11/08/2001	Alexander B. Rossi	A-70882/RMS/AMS	5867

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Robin M. Silva, Esq.
DORSEY & WHITNEY LLP
Suite3400
Four Embarcadero Center
San Francisco, CA 94111-4187

EXAMINER	
QIAN, JANICE LI	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/053,355	ROSSI, ALEXANDER B.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-80* is/are pending in the application.

4a) Of the above claim(s) *40,41,54,55 and 71-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-39,42-53,56-70 and 76-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, drawn to a method of differentiating mucosal mast cells, mast cells produced, and method of using such for screening and species election of screening for small bioactive molecules, is acknowledged. The traversal is on the ground(s) that the subject matter in groups II and III are overlapping, and that a search of these claims can be made without serious burden. This is not found persuasive because it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent methods for making phenotypically different cells using different type of cytokines. For example, cytokine IL-4 will not be used in group II, and IL-6 will not be used in group III; in an abundant art field, this difference would cause a significant increase in literature that need to be searched. As such, the searches for groups III and II would have certain overlap, but they are not co-extensive. M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

In response to the restriction requirement, applicants canceled all original claims and presented new claims in a linking claim format. As a result, claims 37, 42-51, 56-69, and 76-80 now link inventions III and II. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s). Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Applicant is again advised that where a single claim encompasses more than one invention as defined above, upon election of an invention for examination, said claim will only be examined to the extent that it reads upon the elected invention.

Claims 37-80 are pending, however, claims 40, 41, 54, 55, 71-75 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 37-39, 42-53, 56-70, 76-80 are under current examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 51-53, 56-59, 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by *Saito et al* (Int Arch Allergy Immunol 1995;107:63-65, IDS).

Saito et al teach a population of cultured human mast cells using a starting progenitor cell population of 10^7, therefore, *Saito et al* anticipate instant claims.

It is noted that claims 51-53, 56-59 are product-by-process claims. Applicants are reminded that patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). The Office does not have the facilities for examining and comparing applicant's

product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist (or that the claimed products are functionally different than those taught by the prior art) and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPBI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 51-53, 56-58, 64, 65 are rejected under 35 U.S.C. 102(b) as being anticipated by *Kirshenbaum et al* (Blood 1999;94:2333-42, IDS).

Kirshenbaum et al teach a substantially pure population of cultivated human mast cells (see § Materials and methods). Accordingly, *Kirshenbaum et al* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-39, 42-53, 56-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Saito et al* (J Immunol 1996;157:343-50, IDS), taken with *Zhang et al* (Chin J Biotechnol 1999;15:189-94, IDS).

Saito et al teach a method of generating cultured human mast cells comprising contacting CD34+ cells with human stem cell factor and human IL-6 (§Cell culture, page 344), thereby a proliferated population of mast cells are formed (e.g. abstract and fig. 1). The purified CD34+ cells are prepared from human cord blood (§Cell preparation, page 344). They go on to teach that IL-6 enhanced the SF-induced development of tryptase-positive mast cells (left column, page 345), and 99% of cultured cells stained positive for tryptase, and 18% for chymase (2nd paragraph, left column, page 349), thus, roughly 80% cells are mucosal mast cells. *Saito et al* do not teach using flt-3 in the process.

Zhang et al teach the influence of flt-3 on *ex vivo* expansion of hematopoietic stem cells, and concluded that flt-3 synergized with SCF in maintaining the activities of stem/progenitor cells.

Claims 59-63 recite a particular numbers of proliferated population of progenitor cells comprises at least about 10^7 cells. Saito et al use a starting cell population of cells, thus, the proliferated cells would be more than 10^7 cells. Given the knowledge of the skilled, this limitation would fall within the bounds of the optimization for cell culture.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Saito et al,* by simply combining the flt-3 with SCF in preparing the progenitor cells as taught by *Zhang et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method to arrive at the claimed invention because it is known that flt-3 synergizing the effect of SCF in expanding progenitor cells, and it is known SCF and IL-6 could differentiating the stem cells to mast cells, thus, the combination would enhance mast cell production. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 67-70, 76-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Saito et al* (J Immunol 1996;157:343-50), and *Zhang et al* (Chin J Biotechnol 1999;15:189-94) as applied to claims 37-39, 42-53, 56-66 above, and further in view of *Demo et al* (Cytometry 1999;36:340-8) and *Janaki et al* (J Ethonopharmacol 1999;67:45-51).

Saito et al and Zhang et al teach a method of expanding mast cells in vitro. Saito et al also teach that such method overcomes the difficulties in obtaining large quantity of mast cells and thus is very useful in studying the role of mast cells in allergic disorders (last paragraph, page 349). *Saito et al* do not particularly teach a method of using mast cells for potential drug screening.

Demo et al teach a method for studying interaction of mast cells and small molecule drugs comprising monitoring mast cell degranulation upon contacting with a

drug by flow cytometric Annexin-V binding using cultivated mast cell lines derived from rats. They contact mast cells with a bioactive agent such as phosphatidylinostitol 3 kinase inhibitor wortmannin, and determine whether the degranulation of mast cells are altered (see abstract). *Demo et al* do not teach using *human* mast cells.

Janaki et al teach isolating bioactive agene that causes reduced mast cell degranulation from plant cells.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Demo et al,* by substituting the rat mast cells with that of human mast cells or isolating the bioactive agents if necessary with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because when developing a small molecule drug for humans, cells from human origin would be more relevant. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim (64) recitation, "substantially pure". The specification does not provide a standard for ascertaining the requisite degree of "substantially pure", and thus the metes and bounds of the claims are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-39, 42-53, 56-70, 76-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

Claims are drawn to using combination of cytokines flt-3, SCF, and IL-6 for producing mucosal mast cells from CD34+ cells, preferably obtained from cord blood.

The specification teaches that mucosal mast cells contain tryptase but lack chymase and carboxypeptidase (Specification, 2nd paragraph, page 1).

However, the prior art of record is ambiguous regarding the phenotype of SCF/IL-6 generated mast cells. *Matsushima et al* (J Dermatol Sci 2000;24:4-13) teach that using electron microscopic analysis, these cells are so immature that they could not distinguish MCT and MCTC based on the ultrastructural morphology, they concluded that SCF and IL-6 do not develop fully mature mast cells *in vitro* (abstract). *Saito et al* teach, that cultivated population are 99% positive for tryptase, and 18% chymase (2nd paragraph, left column, page 349), thus, it appears that a mixed population is produced. *Ahn et al* (J Allergy Cin Immunol 2000;106:321-8) teach that tryptase-positive cultivated mast cells can give rise to tryptase and chymase double-positive MCs (abstract). *Kinoshita et al* (Blood 1999;94:496-508) teach that SCF/IL-6 would cause substantial increases in the frequency of chymas-positive cells (see abstract). The specification acknowledges such uncertainty and teaches that even though reports from prior art of record such as *Saito et al* teach that SCF and IL-6 could differentiate mast cells from CD34+ cells, reports from different groups indicated that prior methods have produced variable results (Specification, paragraph bridging pages 3-4).

In view of such, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification to clarify the variable results and advance the knowledge lacking in the prior art of record. However, the specification fails to shed light on such ambiguity in the prior art, because it fails to clearly describe the phenotypes or quantity of the progenitor cells and mast cells produced by the claimed method. For

example, whether the mast cells are indeed mature so that the mucosal phenotype could be determined by EM ultrastructures, or whether the generated mast cells have mixed phenotypes as taught by *Saito et al*, and if so, the percentage of double-positive cells vs. tryptase-positive only cells, or whether the tryptase-positive cells would give rise to double-positive cells under the claimed condition. Figures 7a-c and 9 describe CD markers, and the specification teaches that these markers could be positive or negative for both types of mast cells (Specification, page 16). In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references.

Accordingly, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, it would have required undue experimentation for the skilled artisan intending to practice the instant invention.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942 (571-272-0730, after the Office relocation in January, 2004). The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
December 22, 2003